Understanding the role of LRRK2 in iPSC cell models of Parkinson's Disease

Grant Award Details

Understanding the role of LRRK2 in iPSC cell models of Parkinson's Disease

Grant Type:	Basic Biology III
Grant Number:	RB3-02221
Project Objective:	The overarching goal of this work is to utilize stem cell based models of Parkinson's disease (PD) derived from cells of PD affected patients that harbor mutations in the LRRK2 gene so that the deleterious role of mutated LRRK2 in disease can be elucidated. Mutations in LRRK2 are the most common cause of familial PD. The disease presentation for these patients with LRRK2 mutation is typically clinically similar to those with sporadic disease, making the onset of disease due to LRRK2 dysfunction clinically relevant. The team has utilized stem cells harboring a mutation in LRRK2 and also daughter cells of that line in which genomic editing techniques have been applied to correct the PD mutation or disrupt the LRRK2 gene.

Investigator:

Name:	R. Jeremy Nichols
Institution:	Parkinson's Institute
Type:	PI

Disease Focus:	Parkinson's Disease, Neurological Disorders
Human Stem Cell Use:	iPS Cell
Award Value:	$1,482,822
Status:	Closed

Progress Reports

Reporting Period:	Year 1
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Reporting Period:	Year 2
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Reporting Period:	Year 3

View Report

Grant Application Details

Application Title: Understanding the role of LRRK2 in iPSC cell models of Parkinson's Disease

Public Abstract: The goal of this research is to utilize novel research tools to investigate the molecular mechanisms that cause Parkinson's disease (PD). The proposed work builds on previous funding from CIRM that directed the developed patient derived models of PD. The majority of PD patients suffer from sporadic disease with no clear etiology. However some PD patients harbor specific inherited mutations have been shown to cause PD. The most frequently observed form of genetic parkinsonism is caused by the LRRK2 G2019S mutation it the most common. This mutation accounts for approximately 1.5-2% of patients with apparently sporadic PD, increasing to 4-6% of patients with a family history of PD, and even higher in isolated populations. Importantly, LRRK2 induced PD is clinically and pathologically largely indistinguishable from sporadic PD.

This proposal focuses on studying the most frequent cause of familial PD and induces disease that is clinically and pathologically identical to sporadic PD cases. It is likely that LRRK2 regulates a pathway(s) that is important in the more common sporadic form of PD as well. Therefore by employing relevant models of PD, we hope to drive the biological understanding of LRRK2 in a direction that facilitates the development of disease therapeutics in the future. We ascertained patients harboring mutations in LRRK2 [heterozygous (+/G2019S) and homozygous (G2019S/G2019S)] as well as sporadic cases and age matched controls. We have successfully derived iPSCs from each genotype and differentiated these to DA neurons. We will use these as a model system to investigate these LRRK2 based models of PD.

We will adapt current biochemical assays of LRRK2, which are source material intensive, to the small culture volumes required for the differentiation of iPSCs to DA neurons. This is a crucial necessity for development for utilizing iPSC derived DA neurons as tractable models of LRRK2 based PD. We will then probe the roles of LRRK2 in neuronal cell differentiation and survival. We will also ask whether the mutant LRRK2 induces changes in autophagy, as this has been postulated as a mechanism of LRRK2 induced pathogenesis. By studying wild-type and disease mutant LRRK2, in DA models of PD we hope to provide crucial understanding of the role mutant LRRK2 has in disease.

Statement of Benefit to California:

It is estimated that by the year 2030, 75,000-120,000 Californians will be affected by Parkinson's disease. Currently, there is no cure, early detection mechanism, preventative treatment, or effective way to slow disease progression. The increasing disability caused by the progression of disease burdens the patients, their caregivers as well as society in terms of healthcare costs. The majority of PD patients suffer from sporadic disease with no clear etiology, and a in a handful of these patients specific inherited mutations have been shown to cause PD. The most frequently mutated gene is called Leucine Rich Repeat Kinase 2 (LRRK2). Our goal is to study the mutated gene product in patient based models of Parkinson's disease.

In previous CIRM funding, we have developed patient derived induced pluripotent stem cells (iPSCs) from patients harboring mutations in LRRK2. We have been successful in differentiating populations these iPSCs into the neurons that are depleted in PD. The next step is to utilize these cells as models of mutation induced PD 'in a dish'. We will employ these pertinent disease models to answer basic biology questions that remain about the function of LRRK2.

This project brings together scientists previously funded by CIRM with scientists well versed in the study of LRRK2. This multidisciplinary approach to studying the causes of PD is a natural benefit to the State of California and its citizens. By bringing a better understanding of the role of LRRK2 in the cells that are lost in the progression of PD, we will bring more concrete knowledge of PD as a whole, bringing more hope for the development of a therapeutic for disease.

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